

# ***Enterobacter sakazakii* Infections Associated with the Use of Powdered Infant Formula --- Tennessee, 2001**

*Enterobacter sakazakii*, a gram-negative, rod-shaped bacterium, is a rare cause of invasive infection with high death rates in neonates (1,2). This report summarizes the investigation of a fatal infection associated with *E. sakazakii* in a hospitalized neonate, which indicated that the infection was associated with the presence of the organism in commercial powdered formula fed to the infant. The implicated batch of formula has been recalled by the manufacturer. Clinicians should be aware of the potential risk for infection from use of nonsterile enteral formula in the neonatal health-care setting.

In April 2001, a male infant (2 lbs, 13 oz [1,270 grams]) was delivered by cesarean section at 33.5 weeks' gestation and was hospitalized in a neonatal intensive care unit (NICU) because of low birthweight, prematurity, and respiratory distress. The infant had fever, tachycardia, decreased vascular perfusion, and neurologic abnormalities (e.g., suspected seizure activity) at 11 days. Cerebrospinal fluid (CSF) obtained by lumbar puncture was analyzed and revealed a white blood cell count of 32/mm<sup>3</sup> [normal=0--0.5/mm<sup>3</sup>], red blood cell count of 27/mm<sup>3</sup> [normal=0], protein of 292 mg/dL [normal=15--45 mg/dL], and glucose of 1 mg/dL [normal= 40--70 mg/dL]. Culture of CSF grew *E. sakazakii*. The infant was treated with intravenous antimicrobials for meningitis; however, neurologic damage was progressive, and the infant died 9 days later. Because the organism was a rare cause of neonatal meningitis, hospital personnel, in collaboration with the Tennessee Department of Health and CDC, investigated the source of infection.

During April 10--20, 2001 (i.e., the study period), enhanced case surveillance was performed to determine if other infants in the NICU were either infected or colonized with *E. sakazakii*. Patients were assessed for colonization by stool culture; microbiology laboratory records also were reviewed for reports of *E. sakazakii* growth from clinical specimens during the study period. Confirmed infection was defined as any *E. sakazakii*-positive culture from a normally sterile site. Suspected infection was defined as an *E. sakazakii*-positive culture from a nonsterile site with documented deterioration in clinical status (e.g., increased respiratory rate without other evident cause) in the 24 hours before collection of the specimen for culture. Colonization was defined as an *E. sakazakii*-positive culture from a nonsterile site without documented deterioration in clinical status in the 24 hours before collection of the specimen for culture. A total of 49 infants were screened. Ten *E. sakazakii* infection or colonization events were identified: one confirmed infection in the index patient (culture-positive from CSF), two suspected infections (both culture-positive from tracheal aspirate), and seven colonizations (six culture-positive from stool, one from urine). One patient was colonized at two sites (urine and stool).

A cohort study was performed on the 49 patients who were screened to determine possible risk factors for acquisition of *E. sakazakii* infection or colonization. A case-patient was defined as any NICU patient with *E. sakazakii* infection (confirmed or suspected) or colonization during the study period. Medical records were reviewed to assess possible risk factors during the study period, including gestational age, birthweight, mechanical ventilator use, humidified incubator use, oral medications, and feeding type (total parenteral nutrition, formula [e.g., powdered or liquid], or breast milk) or method (i.e., continuous or intermittent administration). Of the 49 patients identified in the cohort, nine were case-patients and 40 were noncase-patients. Analysis of risk factors identified only use of a specific powdered infant formula product (Portagen [Mead Johnson Nutritionals, Evansville, Indiana]) to be significantly associated with *E. sakazakii* infection or colonization; all case-patients received Portagen compared with 21 of 40 noncase-patients ( $p < 0.01$ ).

To determine the source of infection, microbiologic studies were performed on samples of commercially sterile water used for formula preparation and from samples of formula taken from opened cans of Portagen from the same two batches used in the NICU during the study period. Environmental swab cultures were taken from surfaces on which the product had been prepared. Cultures also were performed on unopened containers of Portagen supplied by the manufacturer with batch codes matching those of opened cans. The water was cultured using membrane filtration. The powdered infant formula was cultured using a modification of a previously described enrichment method (3). Specifically, for each culture of formula, 100 grams of Portagen were inoculated in phosphate-buffered peptone water, incubated overnight, subcultured, reincubated, and picked and streaked. Colonies that demonstrated a yellow pigment characteristic of *E. sakazakii* were then picked for identification. Cultures of formula taken from both opened and unopened cans of Portagen from a single batch grew *E. sakazakii*. Water and all environmental cultures were negative. Pulsed-field gel electrophoresis revealed that isolates of *E. sakazakii* from the CSF culture of the neonate with meningitis and from the culture of formula from both opened and unopened containers were indistinguishable.

Hospital personnel reviewed NICU infection-control practices, policies, and procedures for preparation, storage, and administration of powdered infant formula. No breaches in infection control were detected. The product was prepared in the NICU according to manufacturer's instructions. Powdered formula was mixed with sterile water and was immediately refrigerated and used within 24 hours of preparation. The infant with *E. sakazakii* meningitis was given formula by continuous administration; administration or "hang" time (i.e., the amount of time the contents of a formula bag are fed to a patient) did not exceed 8 hours.

To prevent additional infections, the hospital made several policy changes. Principal formula type for NICU patients was changed from powdered formula to a commercially sterile, ready-to-feed liquid formula. Portagen is no longer used; other powdered formula products are reserved for specific needs and, when necessary, are prepared in a designated formula preparation room in the pharmacy. The amount of allowable administration or "hang" time has been reduced from 8 hours to 4 hours. As of April 10,

2002, no additional episodes of infection or colonization have been detected at the reporting hospital.

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### **Editorial Note:**

This report describes an association between fatal infection attributed to *E. sakazakii* and use of a commercial powdered infant formula in a NICU. *E. sakazakii* is a rare cause of invasive disease in neonates; however, when meningitis occurs, severe neurologic complications, including cerebral abscess formation, are common, and death occurs in 33%--80% of cases (1,2). *E. sakazakii* infection, including sepsis, meningitis, or necrotizing enterocolitis, has been associated with use of powdered infant formula (4--7). In previous studies and in this report, the organism was detected in either prepared formula, the environment in which it was prepared, or unopened products. This is the first report of *E. sakazakii* infection associated with infant formula prompting recall of a commercial product in the United States. Portagen is a type of formula recommended by the manufacturer for infants with nutritional malabsorption problems and is to be used under the supervision of a health-care provider. The batch of Portagen implicated in this investigation (coded BMC17) was recalled voluntarily by Mead Johnson Nutritionals on March 29, 2002 (8). The manufacturer has disseminated a letter to health-care providers about the risk of powdered infant formulas.

Proper handling and use of infant formula products in the health-care setting is an important patient safety issue. Clinicians should be aware that powdered formulas are not sterile products and might contain opportunistic bacterial pathogens such as those in the family *Enterobacteriaceae*, including *E. sakazakii* (3). These products commonly are used at many hospitals. A recent survey indicated that of 16 responding facilities, nine used powdered formulas in the NICU setting; four (25%) reported powdered formula as a principal source of patient feeding, and five (31%) reported use of powdered formula along with other formula types for principal feeding (National Association of Children's Hospitals and Related Institutions, unpublished data, 2001).

Risk for infection might depend on several factors, including the number of bacteria present in the product, handling after preparation, and underlying patient characteristics (e.g., immunosuppression, prematurity, or low birthweight). Because powdered formula is not sterile and can provide a good medium for growth, prolonged periods of storage or administration at room temperature might amplify the amount of bacteria already present. Health-care providers might be able to reduce risks for hospitalized neonates by choosing alternatives to powdered forms when possible. Preparation of formula should follow manufacturer's instructions, which might require steps beyond those described on the product label. The American Dietetic Association (ADA) has published guidelines for appropriate formula use, including details concerning proper preparation, storage, and

administration (9). On the basis of these guidelines and input from ADA and the Food and Drug Administration (FDA), interim recommendations have been proposed concerning preparation of powdered infant formula in the NICU setting [see [box](#)]. In addition, FDA has disseminated a letter to health-care providers with further recommendations (10).

Health-care providers should report invasive disease attributed to *E. sakazakii* in infants aged <12 months, particularly bloodstream infection or meningitis with onset in the health-care setting, to state health departments and CDC (800-893-0485); adverse events associated with infant formula should be reported to FDA's MedWatch program (800-332-1088 or at <http://www.fda.gov/medwatch>).

## Acknowledgments

Office of Field Programs, Office of Scientific Analysis and Support, Office of Field Products, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration. S Robbins, American Dietetic Association. D Ben-Avram, American Society for Parenteral and Enteral Nutrition. C Braden, R Tauxe, Div Bacterial and Mycotic Diseases, National Center for Infectious Diseases; A Shane, EIS Officer, CDC.

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## Box

### Summary Interim Recommendations for Preparation of Powdered Infant Formula in the Neonatal Intensive Care Unit Setting

1. Formula products should be selected based on nutritional needs; alternatives to powdered forms should be chosen when possible.
2. Trained personnel should prepare powdered formula under aseptic technique in a designated preparation room.
3. Manufacturer's instructions should be followed; product should be refrigerated immediately and discarded if not used within 24 hours after preparation.
4. The administration or "hang" time for continuous enteral feeding should not exceed 4 hours.
5. Written hospital guidelines should be available in the event of a manufacturer product recall, including notification of health-care providers, a system for reporting and follow-up of specific formula products used, and retention of recall records.

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